

IN THE EUROPEAN PATENT OFFICE

Applicant: Omeros Corporation, et al.

European Application No: 00 947581.5

Int'l. Filing Date: 21 July 2000 (21.07.00)

Title: SOLUTIONS AND METHODS FOR INHIBITION OF PAIN, INFLAMMATION
AND CARTILAGE DEGRADATION

Agent's File Reference No. APEP01999

DECLARATION OF STEVEN B. ABRAMSON, M.D.

I DO HEREBY SOLEMNLY AND SINCERELY DECLARE AS FOLLOWS:

1. I, Steven B. Abramson, M.D., am a Professor of Medicine and Pathology, and Chairman of the Departments of Rheumatology and Medicine, at the Hospital for Joint Diseases, New York University School of Medicine, New York, NY, USA. I obtained my Medical Degree from Harvard University, completed my residency at NYU Medical Center – Bellevue Hospital, and am certified by the American Boards of Internal Medicine and Rheumatology. I am, and for the last 25 years have been, active in research, clinical trials and practice in specialties including rheumatic diseases, osteoarthritis and other joint diseases. I have authored or co-authored over 80 publications in refereed journals in these fields, as well as numerous books, and serve on the editorial boards of the journals *Arthritis & Rheumatism* and *Journal of Rheumatology*. As part of my academic, research and hospital responsibilities, I supervise and train academicians and clinicians of less experience in my specialties. My *curriculum vitae*, including a bibliography of publications, is attached.

2. I have reviewed and am familiar with the disclosure and claims contained in European Patent Application 00 947581.5 (the "Application"), corresponding to International Patent Application PCT/US00/19864. I have been asked to express my opinions regarding certain scientific terms used in the Application. These terms include: "chondroprotective agent"; "anabolic chondroprotective agents" (also referred to in the Application as "agents that promote cartilage anabolism"); and "inhibitors of cartilage catabolism" (also referred to in the Application as "agents that inhibit unregulated or excess cartilage catabolic processes"). Specifically, I was asked to express my opinion on whether these terms would have been readily understood and considered to be definite by one of ordinary skill, experience and expertise in the relevant

scientific field, in view of the disclosure set forth in the Application, and based on public knowledge available to such individuals as of 21 July 1999. I was also asked whether such individuals would readily be able to determine whether a given therapeutic agent was an anabolic chondroprotective agent, or an inhibitor of cartilage catabolism, in view of the disclosure set forth in the Application, and using public knowledge available to such individuals as of 21 July 1999, without undue experimentation.

3. I provide the following opinions based on my personal knowledge and in view of the disclosure set forth in the Application.

a. The term "chondroprotective agent" can encompass agents that either inhibit cartilage degradation (i.e., inhibitors of catabolic processes), enhance cartilage matrix synthesis (i.e., anabolic agents), or both. A discussion of this concept can be found in Altman, et al., Future therapeutic trends in osteoarthritis, *Scand J Rheumatol Suppl* 77:37-42 (1988).

b. The term "chondroprotective agent" is frequently used in the literature, dating at least to the mid- to late 1980's. The article cited above (Altman et al. (1988)) is one of many that indicate that the concept of chondroprotection has been central to disease modifying strategies in osteoarthritis for over a decade.

c. One of ordinary skill in the field of musculoskeletal disease (e.g., rheumatologists, orthopedists, scientists) would be able to determine whether an agent has anabolic, or catabolic inhibitory, properties, based on the definitions referred to in paragraph (a) above.

d. The term "inhibitor of cartilage catabolism" is well described in the literature and is recognized by those of ordinary skill. Examples include inhibitors of metalloproteinases, interleukin-1 and nitric oxide. I coauthored a review in this area that addresses these issues, based on many references published prior to 1999: Pelletier, J. P., Martel-Pelletier, J., Abramson, S. B., Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets, *Arthritis Rheum.* 44(6):1237-47 (2001).

e. One should be able to determine without undue experimentation that an agent is an inhibitor of cartilage catabolism. References prior to 1999 are cited in the above review article (Pelletier et al. (2001)) that exemplify methodologies for this determination.

f. The term "anabolic agent" is well described in the literature. The fact that anabolic agents increase the production of Type II collagen and proteoglycan is recognized by those of ordinary skill, and therefore the term "anabolic chondroprotective agent" is recognized by those of ordinary skill. Examples of such agents include TGF-B, IGF-1 and selected BMPs.

g. One should be able to determine without undue experimentation that an agent is an anabolic chondroprotective agent with respect to its effect on cartilage metabolism. One of many references prior to 1999 include: Verschure P. J., Van Noorden C. J., Van Marle J., Van den Berg W. B., Articular cartilage destruction in experimental inflammatory arthritis: insulin-like growth factor-1 regulation of proteoglycan metabolism in chondrocytes, *Histochem J* 28(12):835-57 (1996).

h. The Application accurately describes agents that would be expected to be chondroprotective that are inhibitors of cartilage catabolism, or that have anabolic properties.

i. Conventional chondroprotective therapy prior to July 21, 1999 did not to my knowledge employ the local administration (e.g., intraarticular injection) of a combination of anabolic and anti-catabolic agents. Based on the disclosure in the Application and subsequent developments, I expect this combination would be more effective than the injection of either agent alone.

4. I make this solemn declaration conscientiously and sincerely believing the same to be true.

5. In the event that a copy of this declaration should ever be filed in any corresponding United States Patent Application, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful, false statements and the like that are so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

DATED this 20 day of April, 2003.



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CURRICULUM VITAE

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Date of Birth: January 24, 1948 Place of Birth: Port Chester, N.Y., U.S.A.

EDUCATION:

1970 A.B. Dartmouth College, Hanover, NH
1974 M.D. Harvard Medical School, Boston, MA

PROFESSIONAL TRAINING:

1974-1977 Intern, Resident, NYU Medical Center-Bellevue Hospital
1977-1978 Chief Resident in Medicine, NYU Medical Center-Bellevue Hospital
1978-1980 Fellow, Chief Fellow, Division of Rheumatology,
Department of Medicine, NYU Medical Center-Bellevue Hospital
1980-1983 Postdoctoral Fellow, Research Laboratory,
Division of Rheumatology, NYU Medical Center-Bellevue Hospital
1983-1986 Postdoctoral Fellow, National Arthritis Foundation

ACADEMIC APPOINTMENTS:

1979-1981 Instructor in Medicine, NYU School of Medicine
1981-1985 Assistant Professor of Medicine, NYU School of Medicine
1985-1996 Associate Professor of Medicine, NYU School of Medicine
1996- Professor of Medicine, NYU School of Medicine
1997- Professor of Medicine and Pathology, NYU School of Medicine

HOSPITAL AND MEDICAL SCHOOL APPOINTMENTS:

1981-2001 Firm Chief, Department of Medicine, NYU School of Medicine
1985- Co-Director, Rheumatology Fellowship Training Program,
NYU Medical Center-Hospital for Joint Diseases
1989- Chairman, Department of Rheumatology, Hospital for Joint Diseases
1990- Chairman, Department of Medicine, Hospital for Joint Diseases
1990-1998 Associate Dean for Curriculum, NYU School of Medicine
1994- Physician-in-Chief, Hospital for Joint Diseases
1995 Director, Division of Rheumatology, NYU Downtown Hospital
1998-2001 Vice Dean for Medical Education, NYU School of Medicine
2000- Director, Division of Rheumatology, NYU School of Medicine

AWARDS AND HONORS

Summa Cum Laude, Dartmouth College
Senior Fellow, Dartmouth College
Phi Beta Kappa
Alpha Omega Alpha

Janice Wiles Memorial Lecture on Systemic Lupus Erythematosus, University of Massachusetts, 1997.

Duke University Visiting Professor "Award for Excellence in Immunology," 1999.

Boland Visiting Professor 1999, Mayo Clinic, Rochester, MN.

National Arthritis Foundation Postdoctoral Fellowship Program "Hero", 2001.

LICENSURE AND BOARDS:

1975	Licensed, New York State
1977	Certified, American Board of Internal Medicine
1980	Certified, American Board of Rheumatology

EDITORIAL BOARDS:

1993 - 1997	Editorial Board, Arthritis & Rheumatism
1998 -	Editorial Board, Journal of Rheumatology
2000-	Associate Editor, Osteoarthritis and Cartilage
2000 -	Associate Editor, Arthritis & Rheumatism
2001-	Contributing Editor, JointandBone.org

MAJOR COMMITTEE ASSIGNMENTS, ETC.:

Medical School:

1981-1991	Director, Second Year Medical School Course: "Introduction to Clinical Medicine/Pathophysiology"
1987-	Curriculum Committee
1990-	AOA Selection Committee
1992-1993	Chair, Self Study Task Force, Liaison Committee on Medical Education Re-accreditation of NYU School of Medicine
1995-1996	Chair, Task Force on Curriculum Policy
2002-	Executive Advisory Committee of the NYU School of Medicine General Clinical Research Center

Local Professional:

1987-1993	Medical Advisory Board, The S.L.E. Foundation, Inc.
1990-1991	President, New York Rheumatism Association
1991-1997	Council Member, American College of Rheumatology, Northeastern Region
1992-1993	Program Chairman, Northeast Regional Meeting, American College of Rheumatology, Spring 1993
1993-1994	Chairman, Search Committee for Orthopaedic Chair of the Hospital for Joint Diseases
1993-1998	Chairman, Medical and Scientific Committee,

1993-1998 New York Chapter of the Arthritis Foundation
Vice-President, Board of Governors, New York Chapter of the Arthritis Foundation
1998- Chairman, Executive Committee, New York Chapter of the Arthritis Foundation

National and International Professional:

1994-1997 Scientific and Medical Committee, Arthritis Foundation
1994-1997 Chairman, Inflammation Study Group, American College of Rheumatology
1995-1998 Biochemistry Study Section of the Arthritis Foundation
1995- Arthritis Advisory Committee, Center for Drug Evaluation and Research, Food and Drug Administration (FDA)
1996-1999 Professional Meetings Committee, American College of Rheumatology
1996-1999 Chair, Basic Science Symposia, American College of Rheumatology
1997- Board Trustee, National Arthritis Foundation
1997- International Study Group on COX-2 Inhibitors
1998-1999 Chair, Abstract Selection Committee, 1999 American College of Rheumatology National Meeting
1998-2000 Chairman, Arthritis Advisory Committee, Center for Drug Evaluation and Research, Food and Drug Administration (FDA)
2000- Consultant, Arthritis Advisory Committee, Center for Drug Evaluation and Research, Food and Drug Administration (FDA)
2000- Board of Directors, Osteoarthritis Research Society International
2002- Member, American Board of Internal Medicine (ABIM), Subspecialty Board in Rheumatology

PROFESSIONAL SOCIETIES:

American College of Rheumatology
Harvey Society
American Federation for Clinical Research
Association of Subspecialty Physicians
Osteoarthritis Research Society International (OARSI)

MAJOR RESEARCH INTERESTS:

1. The Role of Nitric Oxide and Prostaglandins in Inflammation and Immunity
2. Complement Activation and Immune Injury in Autoimmunity
3. Inflammatory Mediators Produced by Articular Cartilage